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Clinical impact of lymphatic spread in patients with limited-stage upper aerodigestive tract NK/T cell lymphoma

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Background
We investigated whether distance$_{max}$, that is, the degree of distance between the upper aerodigestive tract (UAT) mass and the farthest pathologic lymph node, was significantly associated with survival in patients with limited-stage UAT natural killer/T cell lymphoma (NKTCL).

Methods
A total of 157 patients who received chemotherapy (CTx) with/without radiotherapy (RTx) were enrolled.

Results
In the survival analysis, an elevated lactate dehydrogenase level [progression-free survival (PFS): hazard ratio (HR), 2.948; 95% confidence interval (CI), 1.606–5.404; $P<0.001$; overall survival (OS): HR, 2.619; 95% CI, 1.594–4.822; $P=0.003$], short distance$_{max}$ (PFS: HR, 0.170; 95% CI, 0.071–0.410; $P<0.001$; OS: HR, 0.142; 95% CI, 0.050–0.402; $P<0.001$), and CTx combined with RTx (HR, 0.168; 95%CI, 0.079–0.380; $P<0.001$; OS: HR, 0.193; 95% CI, 0.087–0.429; $P<0.001$) had an independent predictive value for PFS and OS.

Conclusion
The evaluation of the degree of lymphatic spread and local control by CTx combined with RTx is essential in patients with limited-stage UAT NKTCL.

Key Words Upper aerodigestive tract, Radiotherapy, Natural killer/T cell lymphoma

INTRODUCTION

Extranodal (EN) nasal-type natural killer/T-cell lymphoma (NKTCL) is a rare but aggressive T-cell lymphoma [1-3]. The epidemiology of this disease has significant geographical variation, with a higher incidence in East Asian and Latin American populations [4].

An EN NKTCL can be further classified according to the anatomic sites of the primary mass: a nasal type NKTCL, involving the upper aerodigestive tract (UAT) and an extra-nasal NKTCL, involving the sites outside the UAT [5]. The UAT NKTCL has well-defined morphological, genetic, and clinical characteristics. It has several clinical features such as angioinvasion, tumor necrosis, and frequent association with Epstein-Barr virus, predilection for young males, and more importantly, early-stage detection of most nasal types of NKTCLs [6-8].

Approximately 80% of NKTCLs are localized. In recent years, it has attracted increasing attention, and consensus on treatment has gradually been established. However, there is no standard staging system to date. The Ann Arbor (AA) staging system, which was originally designed for Hodgkin lymphoma, is conventionally used for NKTCLs. However, this staging method has limited utility in prognostication and treatment decision-making in patients with NKTCL, as the NKTCL is almost exclusively EN and the majority is localized at diagnosis. Thus, the AA staging system has

a fatal problem for staging localized UAT NKTCLs. Moreover, the staging of the lymphatic spread in the AA staging system is divided depending on the diaphragm; thus, it is not valuable for localized NKTCLs.

The prognostic impact of the International Prognostic Index (IPI) has been controversial for UAT NKTCLs due to heterogeneous data from several studies [9-12]. In particular, a small population of patients with UAT NKTCL is only included in the high IPI score group [10-14]. Therefore, it might be an inappropriate prognostic system for localized UAT NKTCLs.

Kim *et al.* [15] classified the nasal type UAT NKTCL into limited disease [AA stage I/II without local tumor invasiveness (LTI)] and extensive disease (stage I/II with LTI and stage III/IV). However, recent data have demonstrated that regional lymph node (LN) involvement in the limited stage is significantly associated with poor prognosis in UAT NKTCLs [16]. Moreover, a single data set proposed the tumor, node, and metastasis (TNM) stage in nasal NKTCLs, likely head and neck cancer [17]. In the data, the authors classified patients into no, unilateral, and bilateral LN involvement, as the prognosis in the three groups was significantly different. Thus, no, unilateral, and bilateral involvement was defined as N0, N1, and N2 stage, respectively in the TNM stage of nasal NKTCL.

However, a recent multicenter study showed that the overall survival (OS) did not differ significantly between patients with and without regional LN involvement because of improved local control due to the early use of concurrent chemoradiotherapy [18]. Thus, we hypothesized that the degree of lymphatic spread might have a prognostic significance in limited-stage UAT NKTCLs because advanced spreading of LN involvement could make proper control and treatment of the disease more difficult.

In the present study, we investigated the clinical impact of the degree of the distance between the UAT EN mass and the farthest pathologic LN. Based on a comparative analysis with other available prognostic factors, it is important to predict survival in patients with limited-stage UAT NKTCL.

MATERIALS AND METHODS

Patient eligibility

Between January 2008 and October 2017, 157 patients with AA stage IE and IIE UAT NKTCLs were enrolled at five medical centers: Hanyang University Hanmaeum Changwon Hospital, Pusan National University Hospital, Dong-A University Hospital, Busan Paik Hospital, and Busan Haeundae Paik Hospital. Approval for the retrospective review of electronic medical records was obtained from the Institutional Review Boards of the medical centers.

Diagnosis of an EN NKTCL was made based on the presence of relevant histologic findings and immunophenotypes, such as CD3+, CD20-, and CD56+ with or without positive Epstein-Barr virus by fluorescence in situ hybridization. Moreover, the patients were required to be in a limited stage (AA stage I and II without LTI) and previously untreated with no previous concomitant malignancies, and the primary tumor was required to be located in the UAT. Patients with active pulmonary tuberculosis, viral hepatitis, rheumatoid arthritis, and chronic renal disease were excluded. Tumor response was assessed using the standard response criteria [19].

Immunohistochemistry study

Immunohistochemistry studies were performed on 3-μm-thick sections obtained from formalin-fixed, paraffin-embedded samples. Histological staining with Ki-67 (1:100 clone 7B11, Zymed Lab Inc., San Francisco, CA, USA) antibodies was performed using the standard avidin-biotin-peroxidase complex method as described elsewhere. Heat-induced antigen retrieval was performed for 45 min in a Tris–ethylenediaminetetraacetic acid buffer at pH 8 for the antibody in a pressure cooker at 95°C. The cut-off value for Ki-67 expression was 70%. High expression was defined as a Ki-67 expression level $\geq$70%.

18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scan and the quantitative analysis

Dual-modality 18F-FDG PET/CT was performed using a Biograph instrument (Siemens Medical Solutions, Hoffman Estates, IL, USA) based on dual-slice helical CT and full-ring PET tomography.

PET images were evaluated to detect areas with increased FDG tracer uptake. The lymphoma area with an increased FDG tracer uptake [standard uptake value (SUV) $\geq$2.5] in a contouring border, and a pathologic lesion diameter $\geq$1.0 cm was considered as an active lymphoma lesion. In the PET/CT imaging sections, CT scans were used for PET attenuation correction.

Distance$_{max}$ was defined as the linear distance between the main UAT mass and the farthest pathologic LN in sagittal, coronal, and transverse sections of the initial PET/CT scan; thus, we measured the length of the distance$_{max}$. Distance$_{max}$ in stage I was defined as zero because we did not measure the distance. Furthermore, SUV$_{max}$ was defined as the highest SUV among the maximum value of SUV in each tumorous area or LN measured by PET/CT scan. The SUV$_{max}$ values were also measured in the initial PET/CT.

Statistical analysis

A chi-square test or Fisher's exact test was used as appropriate to analyze categorical variables. A Cox proportional hazard regression model was used to identify independent risk factors for survival in patients with limited-stage UAT ENKTCL.

Progression-free survival (PFS) was calculated from the date of diagnosis to the date of progression, relapse, or the last follow-up date. The OS was measured from the date of diagnosis to the date of death due to the tumor or the last follow-up date. The Kaplan-Meier method was used

to derive the PFS and OS curves. Differences in the survival curves were calculated using the log-rank test.

Receiver operating characteristic (ROC) curves were prepared to estimate the measurement accuracy of the optimal cut-off values of continuous variables such as $distance_{max}$ and SUV_{max}. Statistical analysis was performed using SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA). Statistical significance was set at $P<0.05$.

Table 1. Baseline characteristics of patients with limited stage natural killer/T cell lymphoma.

Characteristics	N (157)
Age	
Median (range)	58 (37–78)
≥60 yr (%)	71 (45.2)
<60 yr (%)	86 (54.8)
Sex	
Male (%)	108 (68.8)
Female (%)	49 (31.2)
Primary site	
Nasal cavity (%)	117 (74.5)
Nasopharynx (%)	34 (21.7)
Oral cavity/oropharynx (%)	6 (3.8)
Ann-Arbor stage	
Stage I	20 (12.7)
Stage II	137 (87.3)
Lactate dehydrogenase	
≥Upper normal limit (%)	31 (19.7)
Normal (%)	126 (80.3)
Ki-67 value	
≥70% (%)	25 (15.9)
<70% (%)	127 (84.1)
B symptoms	
Present (%)	40 (25.5)
Absent (%)	117 (74.5)
ECOG performance status	
Grade 0–1 (%)	114 (72.6)
≥Grade 2 (%)	43 (27.4)
Bulky disease (≥7.5 cm)	
Present (%)	16 (10.2)
Absent (%)	141 (89.8)
Bilateral RLN involvement	
Present (%)	35 (22.3)
Absent (%)	122 (87.7)
Therapeutic modality	
Chemotherapy only (%)	81 (51.6)
Chemotherapy with radiotherapy (%)	76 (48.4)
18F-FDG PET/CT scan	
SUV_{max}, median (range)	8.9 (2.7–41.0)

Abbreviations: 18F-FDG, 18F-fluorodeoxyglucose; ASCT, autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; PET/CT, positron emission tomography/computed tomography; RLN, regional lymph node; SUV_{max}, maximum standard uptake value.

RESULTS

Patient characteristics

The baseline characteristics of the 157 patients with limited-stage UAT ENKTCL are summarized in Table 1. One hundred and eight men (68.8%) and 49 women (31.2%) with a median age of 58 years (range, 29–78 yr) were included in this study. The primary sites of lymphoma were the nasal cavity in 117 patients (74.5%), nasopharynx in 34 (21.6%), and oral cavity/oropharynx in 6 (3.8%). A total of 20 patients (12.7%) were in AA stage I, while 137 patients (87.3%) were in stage II. A total of 31 patients (19.7%) had elevated lactate dehydrogenase levels, and 25 patients (15.9%) had elevated Ki-67 scores above 70%. Furthermore, information about the presence of B symptoms, Eastern Cooperative Oncology Group (ECOG) performance status (PS), bulky disease, bilateral regional LN involvement, therapeutic modality, and SUV_{max} in PET/CT are also described in Table 1.

Treatment and response assessment

Fifty-nine patients (37.6%) received VIPD therapy (etoposide 100 mg/m^2 on days 1–3, ifosfamide 1.5 g/m^2 on days 1–3, cisplatin 33 mg/m^2 on days 1–3, and dexamethasone 40 mg on days 1–4) with/without RTx. Sixty-eight patients (43.3%) received VPDL therapy (etoposide 100 mg/m^2 on days 1–3, ifosfamide 1.2 g/m^2 on days 1–3, dexamethasone 40 mg IV, and L-asparaginase on days 8, 10, 14, 16, 18, and 20) with/without RTx. Moreover, 16 patients (10.2%) received DeVIC therapy (dexamethasone, etoposide, ifosfamide, and carboplatin) and 14 patients (8.9%) received SMILE therapy (solumedrol, methotrexate, ifosfamide, L-as-

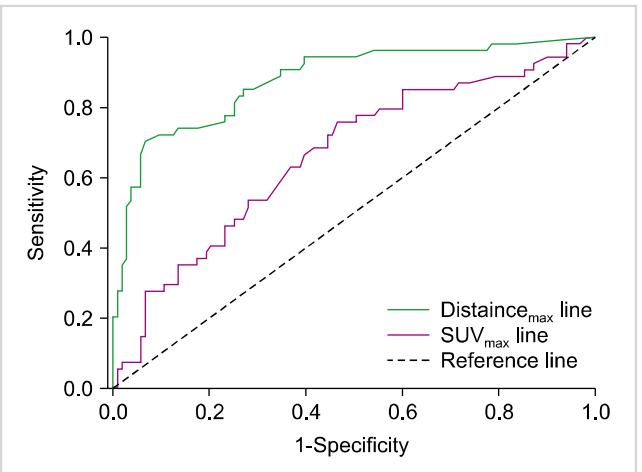

Fig. 1. Receiver operating characteristic (ROC) curves to identify optimal cutoff value of maximum distance ($distance_{max}$) from primary extra nodal site to the farthest lymph node, and maximum standard uptake value (SUV_{max}) in patients with limited stage upper aerodigestive tract natural killer/T cell lymphoma. The calculated optimal cutoffs for $distance_{max}$ and SUV_{max} were 10.8 and 7.1 respectively. In addition, the area under the ROC curve (AUC) values for $distance_{max}$ and SUV_{max} were 0.874 and 0.632, respectively. The AUC value for $distance_{max}$ was significantly higher than that for SUV_{max} ($P<0.001$).

paraginase, and etoposide).

Combined modality treatment schedules included RTx followed by non-anthracycline CTx or non-anthracycline CTx followed by RTx [median cycle, 3 cycles (range, 3–4 cycles)]. The median dose of RTx was 45.0 Gy (range, 38.0–50.0 Gy).

ROC analysis for distance$_{max}$ and SUV$_{max}$

The ROC analysis was performed to measure the optimal cut-off values of distance$_{max}$ and SUV$_{max}$ as continuous variables (Fig. 1). The cut-off values of distance$_{max}$ and SUV$_{max}$ were 10.8 cm and 7.1, respectively. According to the cut-off value of distance$_{max}$, 90 patients (57.3%) were included in the long distance$_{max}$ group, and 67 patients (42.7%) were in the short distance$_{max}$ group. Differences in the PFS and OS between the long and short distance$_{max}$ groups were significant (PFS, $P<0.001$, Fig. 2A; OS, $P<0.001$, Fig. 2B). Furthermore, the high and low SUV$_{max}$ groups were dichotomized using the above cut-off value of SUV$_{max}$. In the analysis, differences in the PFS between the high and low SUV$_{max}$ groups were also very significant ($P<0.001$). However, the OS did not differ between the two groups ($P<0.056$).

Prognostic factors for survivals

We also performed univariate analysis to determine the clinical impact of the other available prognostic factors including male sex (PFS, P=0.059; OS, P=0.458), the presence of B Symptoms (PFS, P=0.568; OS, P=0.504), stage II (PFS, P=0.007; OS, P=0.076), elevated LDH levels (PFS, $P<0.001$; OS, P=0.009), ECOG PS ≥grade 2 (PFS, P=0.003; OS, P=0.016), high Ki-67 levels ≥70% (PFS, P=0.007; OS, P=0.068), regional LN involvement (PFS, P=0.034; OS, P=0.386), bilateral LN involvement (PFS, $P<0.001$; OS, P=0.003), bulky disease ≥7.5 cm (PFS, P=0.531; OS, P=0.334), and CTx combined with RTx (PFS, $P<0.001$; OS, $P<0.001$).

Multivariate analysis was performed on the significant prognostic factors in the univariate analysis. In the analysis, elevated LDH level [PFS: hazard ratio (HR), 2.948; 95% confidence interval (CI), 1.606–5.404; $P<0.001$; OS: HR, 2.619; 95% CI, 1.594–4.822; P=0.003)], short distance$_{max}$ (PFS: HR, 0.170; 95% CI, 0.071–0.410; $P<0.001$; OS: HR, 0.142; 95% CI, 0.050–0.402; $P<0.001$) and CTx combined with RTx (HR, 0.168; 95% CI, 0.079–0.380; $P<0.001$; OS: HR, 0.193; 95% CI, 0.087–0.429; $P<0.001$) had an independent predictive value for PFS and OS (Table 2).

Prognosis according to degree of lymphatic spread and therapeutic modality

We compared prognosis according to distance$_{max}$ as the degree of lymphatic spread and therapeutic modalities such as CTx with/without RTx, since distance$_{max}$ and CTx combined with RTx were independent prognostic factors for survival in patients with limited-stage UAT NKTCL. In the Kaplan-Meier survival curve, lymphoma involvement within a short distance$_{max}$ in patients treated with CTx and RTx had the most favorable PFS and OS (PFS, $P<0.001$; Fig. 3A; OS, $P<0.001$, Fig. 3B). Meanwhile, the involvement within a long distance$_{max}$ in patients who received only CTx had worst PFS and OS (PFS, $P<0.001$; OS, $P<0.001$).

Lymphoma involvement within a short distance$_{max}$ in patients treated with only CTx and a long distance$_{max}$ involvement in patients receiving CTx combined with RTx was an intermediate prognostic group. Differences in survival between the two subgroups were not observed (PFS, P=0.431; OS, P=0.578).

DISCUSSION

In previous studies, most patients with limited-stage UAT NKTCLs have been categorized as low or low-intermediate

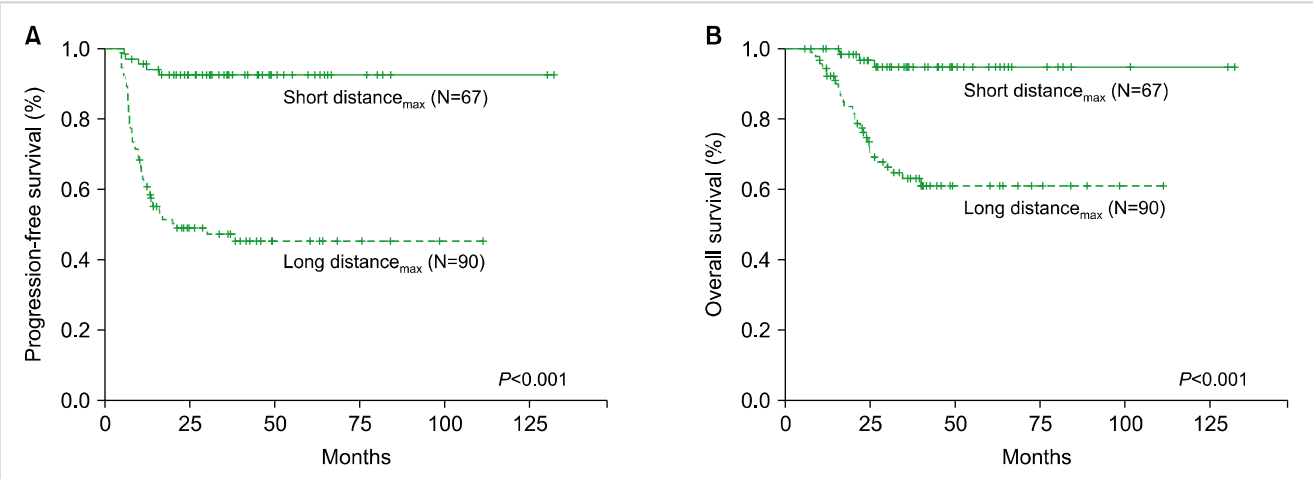

Fig. 2. Survival analysis according to distance$_{max}$ in patients with limited stage upper aerodigestive tract natural killer/T cell lymphoma. Differences in the short distance$_{max}$ group (N=67) and long distance$_{max}$ group (N=90) were significant (progression-free survival, $P<0.001$; Fig. 2A; OS, $P<0.001$; Fig. 2B).

Table 2. Univariate and multivariate analysis of prognostic factors for survival in 157 patients with limited natural killer/T cell lymphoma, nasal type.

	Progression-free survival			Overall survival		
	Univariate	Multivariate		Univariate	Multivariate	
	P	HR (95% CI)	*P*	*P*	HR (95% CI)	*P*
Male sex	0.059	-	-	0.458	-	-
B symptoms	0.568	-	-	0.504	-	-
Age ≥ 60 yr	0.015	0.928 (0.514–1.675)	0.804	0.011	0.943 (0.485–1.835)	0.863
Stage II	0.007	0.965 (0.466–1.999)	0.924	0.076	-	-
LDH > normal	< 0.001	2.948 (1.606–5.404)	< 0.001	0.009	2.619 (1.394–4.822)	0.003
ECOG PS ≥ grade 2	0.003	1.778 (0.959–3.288)	0.068	0.016	2.002 (0.991–4.043)	0.053
High Ki-67 ≥ 70	0.007	1.388 (0.769–2.507)	0.276	0.068	-	-
low SUV_{max} < 7.1	< 0.001	0.538 (0.258–1.126)	0.100	0.056	-	-
Regional LN involvement	0.034	0.627 (0.304–1.290)	0.205	0.386	-	-
Short $distance_{max}$	< 0.001	0.170 (0.071–0.410)	< 0.001	< 0.001	0.142 (0.050–0.402)	< 0.001
Bilateral LN involvement	< 0.001	1.748 (0.980–3.112)	0.059	0.003	2.532 (0.984–4.713)	0.212
Bulky disease (≥ 7.5 cm)	0531	-	-	0.355	-	-
CTx combined with RTx	< 0.001	0.168 (0.079–0.380)	< 0.001	< 0.001	0.193 (0.087–0.429)	< 0.001

Abbreviations: CI, confidence interval; CTx, chemotherapy; $distance_{max}$, maximum distance length; ECOG, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IPI, International Prognostic index; RLN, regional lymph node; RTx, radiotherapy; SUV_{max}, maximum standard uptake value.

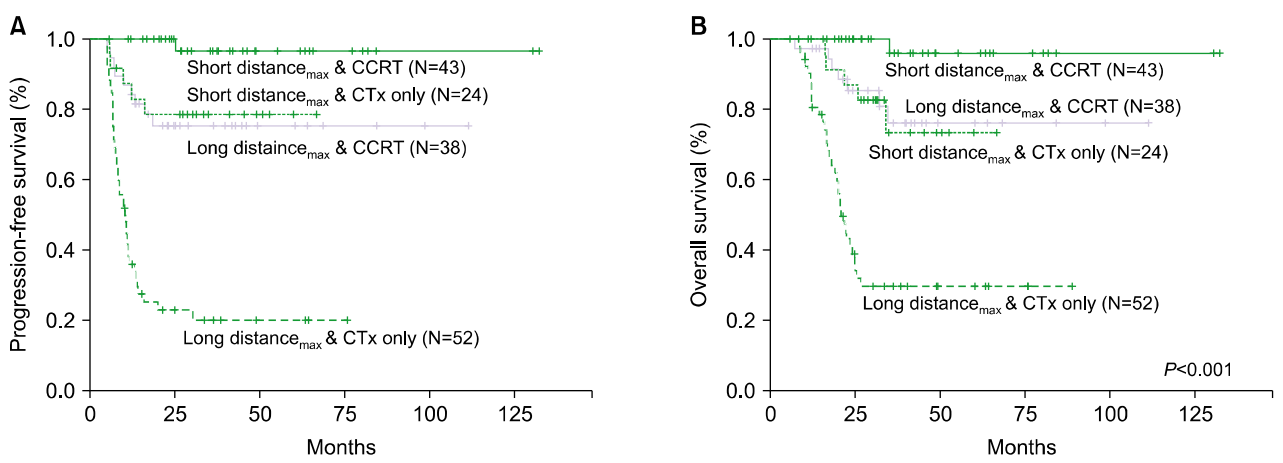

Fig. 3. Prognosis according to degree of lymphatic spread and therapeutic modality. In the Kaplan-Meier survival curve, lymphoma involvement of short $distance_{max}$ in patients treated with CTx and RTx had the most favorable PFS and OS (PFS, $P<0.001$; Fig. 3A; OS, $P<0.001$, Fig. 3B). Meanwhile, involvement of long $distance_{max}$ in patients received only CTx had worst PFS and OS (PFS, $P<0.001$, Fig. 3A; OS, $P<0.001$, Fig. 3B). Lymphoma involvement of short $distance_{max}$ in patients treated with only CTx and long $distance_{max}$ involvement in patients who received chemotherapy combined with radiotherapy did not have significant survival differences (PFS, $P=0.431$; OS, $P=0.578$).
Abbreviations: CCRT, chemo plus radiotherapy; CTx, chemotherapy; $distance_{max}$, maximum distance; OS, overall survival; PFS, progression-free survival; RTx, radiotherapy.

risk using the IPI score [10-14]. Thus, a novel risk stratification model to classify them into a more subdivided risk group than the IPI is required. Furthermore, a study demonstrated that the IPI score could not properly predict complete response and disease-free survival in multivariate analysis [15]. The above findings suggest that other risk stratification models besides the IPI score for predicting survival would be strongly needed in limited UAT NKTCLs.

A previous clinical study proposed the Korean Prognostic Index, which incluses B symptoms, stage, elevated LDH level, and regional LN involvement in an anthracycline-based CTx setting. In particular, the data showed that regional LN involvement is a novel independent risk factor for a worse OS [16]. Meanwhile, another previous study demonstrated that 5-year disease-free survival was shortened in advanced TNM stage in IE/IIE stage lymphoma of the nasal cavity and paranasal sinus [20]. Similarly, other data showed that the TNM stage is correlated with the extent of the disease in lymphoma [21]. In addition, a recent study showed that the TNM stage is more effective in stratifying tumor burden

and risk of prognosis than the AA stage in localized nasal NKTCL [19]. The above data suggest the clinical significance of the TNM staging system in localized UAT area lymphomas. Although the AA staging system could not classify the risk stratification groups, which includes tumor size, invasion to adjacent important structures, and regional LN involvement in the localized NKTCL, it is not thought to be a useful staging system for localized tumors.

Various studies have demonstrated that regional LN involvement is the most important prognostic factor in localized UAT NKTCLs [1, 14, 16, 22, 23]. However, the prognostic index of natural killer cell lymphoma consisting of four risk factors including age, stage, non-nasal type, and distant LN involvement, which was proposed in a recent study, showed that regional LN involvement itself is not significantly associated with survival in NKTCL [18]. We also found that regional LN involvement itself does not properly predict prognosis from parallel analysis with several other risk factors in patients with limited-stage UAT NKTCL. Thus, we measured distance$_{max}$ from the primary EN site to the farthest LN and then analyzed the clinical impact of distance$_{max}$. In the analysis, it was an independent prognostic factor for predicting survival in our patients.

In particular, in the proposed TNM stage in a study of localized nasal NKTCL, N2 stage with bilateral LN involvement had a poorer prognosis than N1 stage with unilateral involvement [17]. However, our study showed that bilateral LN involvement did not significantly reflect the prognosis in limited-stage UAT NKTCLs. This finding suggests that bilateral LN involvement in the radiation field is susceptible to control by RTx or concurrent chemoradiotherapy. For the same reason, shortly involved pathologic LNs were significantly associated with a favorable prognosis in our patients. In contrast, long-distance LN involvement may be beyond the control field. This result suggests that more advanced LN involvement can increase the opportunity for disease progression. Our study showed that lymphoma involvement within a short distance$_{max}$ in patients treated with CTx with RTx had the best prognosis. Meanwhile, the involvement within a long distance$_{max}$ in patients who received only CTx had the worst outcomes.

The present study showed that elevated LDH levels and concurrent chemoradiotherapy were also significant prognostic factors for PFS and OS in patients with limited-stage UAT NKTCLs. Elevated LDH level has been a commonly mentioned significant prognostic factor for predicting survival, and it has also been confirmed as an independent prognostic factor in our data. Moreover, CTx combined with RTx was significantly associated with prognosis. CTx followed by RTx or CTx after RTx showed excellent efficacy of sequential therapies for survival in our patients.

Our study has some limitations, such as its retrospective design, small number of patients, and various CTx regimens. In particular, several CTx regimens may have different short-term efficacies. Generally, some CTx regimens, such as L-asparaginase-containing protocols, could show more favorable short-term efficacy than other therapies. However, there are no clear data showing significant differences in efficacy among several therapeutic regimens. Thus, we did not compare differences in survival according to the CTx regimens.

In the present study, local control by chemo-radiotherapy might also be essential for the treatment of patients. More importantly, we found the clinical significance of distance$_{max}$ reflecting the degree of lymphatic spread for survival in patients with limited NKTCL. We expect that well-designed clinical studies will confirm our findings.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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